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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/209,023	12/10/1998	VIRGINIA E. PATON	P1256R3	8941

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/209,023	Applicant(s) Paton et al.
	Examiner Jennifer Hunt	Art Unit 1642

-- Th MAILING DATE of this communication appears on the c ver she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *8-28-2001 and 9-26-2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9, 12-19, and 34-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9, 12-19, and 34-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 13

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 9-26-2001 has been entered.

2. Acknowledgment is made of applicant's cancellation of claims 20-33 and addition of new claims 34-37. Claims 1-9, 12-19, and 34-37 are pending in the application and considered herein.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in a previous office action.

Claim Rejections Maintained /New Grounds of Rejection

4. Claims 1-9, 12-13, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Oncology, Vol 11, No 3, March 1997, **Norton**, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al.** Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186, in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages

2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996.

Baselga et al teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (page 46 - page 47, column 1) The effective amount of the combination is less than the sum of the effective amounts of the chemotherapeutic agent and antibody individually (page 46, columns 1 and 3) The efficacy of this method is measured by time to disease progression (page 47, column 1).

Norton teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (See pages S10 8- S109, in the Patient Selection section and Table 1)

Lippman et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast, lung (including non-small cell lung), ovarian, thyroid, salivary gland or prostate cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the extracellular domain, and a chemotherapeutic agent. Lippman et al. further teaches various doses as effective to treat the corresponding cancer. Lippman et al. further teaches co-administration of "any chemotherapeutic" which would include non-anthracycline agents.(columns 9 and 26-29)

Hynes et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 extracellular domain, and a chemotherapeutic agent, cisplatin, which is not an anthracycline derivative. Further, Hynes teaches that the antibody acts synergistically therefor the effective amount of the combination of antibody and chemotherapeutic agent is less than the sum of the effective amounts of the antibody and the chemotherapeutic agent individually. (page 178, column 2, paragraph 1).

Arakawa et al. Teaches a method of treating human breast cancer which comprises administering an anti-ErbB2 antibody and a non-anthracycline chemotherapeutic agent, wherein coadministration enhances the therapeutic effect so that the effective amount is less than the

effective amount of the antibody or chemotherapeutic agent when administered individually. (Column 5, line 66-column 6, line 29).

Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al fail to teach the specific chemotherapeutic agent Gemcitabine.

Clemons et al., teaches that as a chemotherapeutic, Gemcitabine has a higher response rate than many other chemotherapeutic agents and looks promising, and that Gemcitabine is effective in combination therapies of breast cancer. (Page 2175, second column and table 8)

Mosconi et al., teaches that Gemcitabine is an effective chemotherapeutic, and ideal for combination therapies, that Gemcitabine is effective and often synergistic in combination therapies of non-small cell lung cancer.(see for example, abstract)

Carmichael et al. I teaches that Gemcitabine is ideal for combination therapy and has low toxicity and high response rate, and that Gemcitabine is effective in combination therapies of breast cancer.(see for example, abstract).

Carmichael et al. II teaches that Gemcitabine is ideal for combination therapy and has low toxicity and high response rate, and that Gemcitabine is effective in combination therapies of breast cancer.(see for example, abstract).

Tsai et al. teaches that Gemcitabine is more effective against cell lines which express high levels of HER2 (see for example, abstract).

Therefor it would have been *primae facie* obvious to one of ordinary skill in the art at the time of applicant's invention to select the specific non-anthracycline chemotherapeutic agent

Gemcitabine in the combination therapies of Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al. and one would have been motivated to do so because Gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. Further, coadministration of antibody and chemotherapeutic agent produces a synergistic therapeutic response, as taught by Hynes et al. Further, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same purpose: idea of combining them flows logically from their having been taught individually in the prior art." In re Kerkhoven (205 USPQ 1069, CCPA 1980).

5. Claims 1-9 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hudziak et al.**, US Patent 5,770,195, and further in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996.

Hudziak et al. teaches a method of treatment of any mammal diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising

administering and effective amount of an anti-ErbB2 antibody which binds the extracellular domain, and a chemotherapeutic agent which is not an anthracycline derivative. Hudziak fails to teach administration to humans or specific chemotherapeutic agent Gemcitabine.

Although Hudziak et al. is silent with respect to the administration of the therapy to human patients, humans would be encompassed by the scope of mammals and the therapy is clearly intended for human use, as the antibody binds a human cell receptor.

Further, Clemons et al., Mosconi et al., Carmichael et al. (I), Carmichael et al. (II) or Tsai et al. teach the desirability of Gemcitabine because of it's low toxicity and high response rate as described supra.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to administer the therapy taught in Hudziak et al. to human patients, and one would have been motivated to do so because all receptors and cytotoxic factors are specific human factors and the treatment was ultimately intended for human use, as taught by Hudziak et al in the background of invention. Further, it would have been primae facie obvious to select the specific non-anthracycline chemotherapeutic agent Gemcitabine in the combination therapies of Hudziak et al., and one would have been motivated to do so because Gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II)or Tsai et al. Further, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same

purpose: idea of combining them flows logically from their having been taught individually in the prior art." In re Kerkhoven (205 USPQ 1069, CCPA 1980).

6. Claims 1-9, 12-13, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al**, Journal of Clinical Oncology, Vol 14, No 3, March 1996, in view of **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996, and further in view of in view of **Hynes et al**, Biochimica et Biophysica Acta, 1994, page 178.

Baselga et al in Journal of Clinical Oncology teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody which binds the 4D5 extracellular domain (page 737, last paragraph). Time to response rate was used to measure efficacy (page 738, last paragraph). Although Baselga et al. fails to teach the administration of the antibody in combination with a chemotherapeutic to humans, it does teach that the antitumor effects of paclitaxel are potentiated by coadministration with the antibody and that this method is currently being administered to humans in clinical trials

(page 743, last paragraph). Baselga et al further fails to teach that the effective amount of the chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually and the selection of the specific chemotherapeutic agent Gemcitabine.

Further, Clemons et al., Mosconi et al., Carmichael et al. (I), Carmichael et al. (II) or Tsai et al. teach the desirability of Gemcitabine because of it's low toxicity and high response rate as described supra.

Hynes et al teaches that coadministration of an anti-ErbB2 antibody and a non-anthracycline derivative chemotherapeutic agent produces a synergistic treatment effect. Therefor the effective amount of the chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to administer the method of Baselga et al to human patients with a reasonable expectation of success and one would have been motivated to do so because administration of antibody is an effective method of treating metastatic breast cancer and coadministration of antibody and paclitaxel enhanced anti-tumor effects, as taught by Baselga et al. Further, coadministration of antibody and chemotherapeutic agent produces a synergistic therapeutic response, as taught by Hynes et al. Further, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same purpose: idea of combining them flows logically from their having been taught individually in the prior art." In re Kerkhoven (205

USPQ 1069, CCPA 1980). It is well known in the art as set forth above that anti-Her2 antibodies and the chemotherapeutic paclitaxel are both useful for inhibiting the growth of tumors. Methods of inhibiting tumor growth by using chemotherapy are well established and therefor it would be obvious to use chemotherapy treatment in combination with an antibody therapy which has been established to be effective. Further, it would have been *primae facie* obvious to select the specific non-anthracycline chemotherapeutic agent Gemcitabine in the combination therapies of Baselga et al.{II}, and one would have been motivated to do so because Gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al.

7. Claims 1-9, 12-19, 34, and 37 under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Journal of Clinical Oncology, Vol 14, No 3, March 1996 (Baselga I), **Baselga et al.**, Oncology, Vol 11, No 3, March 1997 (Baselga II), Norton, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al.** Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186 or **Hudziak et al.**, US Patent 5,770,195, and **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**, European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai**

et al., Cancer Research Vol. 56, pages 794-801, 1996, in view of **Singal at al.**, Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of **Seifert et al.**, The Annals of Pharmacology, Vol 28, September 1998.

Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. teach as applied to claims 1-9 and 12-13 supra. Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. fail to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Baselga

(I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al., into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

It is further noted that the printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

See In re Haller 73 USPQ 403 (CCPA 1947), where it is held that application of printed matter to old article cannot render the article patentable. In the opinion text of In re Haller, it is stated that: Whether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned...In accordance with the patent statutes, an article or composition of matter, in order to patentable, must not only be useful and involve invention, but must also be *new.* If there is no novelty in an article or composition itself, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended. The difficulty is not that there can never be invention in discovering a

new process involving the use of an old article, but that the statues make no provision for patenting of an article or composition which is not, in and of itself, new.

Also see In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. Further, In re Miller 164 USPQ 46 (CCPA 1969) and In re Gulak (CA FC)217 USPQ 401 relate to a mathematical device and to a measuring cup respectively. In each of these cases, the printed matter is considered a patentable distinction because the function of the device depends upon the printed matter itself which is a part of the substrate; without the printed indicia or numbers, the substrates lose their function. Such is not the case with the instantly claimed articles. The antibodies of the claimed articles remain fully functional absent the labeling or printed instructions for use.

It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Thus the instructions for use included in a kit or article manufacture constitute an "intended use" for that kit or article of manufacture.

Intended use does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey, 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, the claims are drawn to an article of manufacture which comprises an anti-HER2 antibody, and labeling instructions. The intended use which is recited on the label or package insert lacks a function relationship to the antibody because the insert or label does not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for other purposes. Therefore the anti-HER2 antibodies which are comprised within the article of manufacture are unpatentable over the prior art anti-HER2 antibodies, because they function equally effectively with or without the labeling, and accordingly *no functional relationship exists between the instructions for use and the antibodies.*

Thus the claims have been addressed as being drawn to an article of manufacture comprising an antibody and a package insert, the instructions on the insert bearing no patentable weight.

8. Claims 1-9 and 12-13, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baselga et al.**, Journal of Clinical Oncology, Vol 14, No 3, March 1996 (Baselga I), **Baselga et al.**, Oncology, Vol 11, No 3, March 1997 (Baselga II), **Norton**, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, **Lippman et al**, US Patent 5,578,482, November 26, 1996, **Hynes et al.** Biochemica et Biophysica Acta 1198, 1994, or **Arakawa et al**, US Patent 5,783,186 or **Hudziak et al.**, US Patent 5,770,195, and **Clemons et al.**, European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, **Mosconi et al.**,

European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, **Carmichael et al.**, European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997 (Carmichael I), or **Carmichael et al.** Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995 (Carmichael II), or **Tsai et al.**, Cancer Research Vol. 56, pages 794-801, 1996, and further in view of **Maier et al.**, Cancer Research, Vol. 51, pages 5361-5369, 1991, or **Lewis et al.**, Cancer Immunol. Immunother, Vol. 37, 1993, and **Van Moorsel et al**, Seminars in Oncology, 42/2, Suppl 7, S717-S723, 1997, or **Hansen**, Ann Oncol., Vol. 7, Suppl. 1, pp29, 1996.

Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. teach as applied to claims 1-9 and 12-13 supra. Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II) or Tsai et al. fail to teach specific treatment of bladder cancer or pancreatic cancer using the combination of methods.

In addition to the teachings set forth above, Hynes et al. teaches that HER2 provides an excellent target for cancer therapy, including using anti HER2 antibodies, in any cancer which over expresses HER2. Hynes et al. further teaches that bladder cancer and non-small cell lung cancer over express HER2 (see page 178 and table 2).

Maier et al. teaches that HER2 is over expressed in many cancers, including breast cancer and pancreatic cancer (see page 5361, column 2).

Lewis et al. teaches that teaches that HER2 is over expressed in many cancers, including breast cancer and pancreatic cancer (see page 256, first column)

Van Moorsel et al. teaches that Gemcitabine is an effective treatment for bladder, pancreatic, non-small cell lung and breast cancer (see for example, abstract).

Hansen teaches that Gemcitabine is an effective treatment for bladder, pancreatic, and non-small cell lung (see entire document).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the treatments of Baselga (I), Baselga (II), Norton, Lippman et al, Hynes et al, Arakawa et al, or Hudziak et al. and Clemons et al., Mosconi et al., Carmichael (I), Carmichael (II), or Tsai et al. to treat any cancer which over expressed HER2, including non-small cell lung cancer, bladder cancer and pancreatic cancer, because these cancers can all over express HER2, as taught by Hynes et al., Maier et al, and Lewis et al., and further any cancer which over expresses HER2 is ideally targeted by HER2 antibody therapies, as taught by Hynes et al, and further that Gemcitabine is also effective for treating non-small cell lung, pancreatic and bladder cancer, as taught by Van Moorsel et al. and Hansen, and also is ideal in combination therapies, as set forth previously.

Arguments

Applicant has argued the rejections together, so applicant's arguments are addressed together. Applicant argues that the instant method produces unexpected results: specifically, the

combination of an anti-ErbB2 antibody and Gemcitabine result in synergistic therapeutic effects. Applicant provides three post filing date articles as evidence of these unexpected results. Applicant thus concludes that the instant invention is not obvious over the prior art in the light these "unexpected results". Applicant's arguments filed 8-28-2001 have been fully considered but they are not persuasive.

The results cited by applicant as "unexpected" are not unexpected, in light of the prior art teachings with regard to HER2 therapies. Showing of additive effect or even synergy is not sufficient to overcome a prima facie case of obviousness, if the results achieved were expected in view of the teachings of the prior art. See MPEP 716.02:

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). In Corkhill, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L- aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.).

It is well known in the art that HER2 combination therapies exhibit synergy (see for example Hynes et al. (page 178), or Baselga I (page 46)). The synergy is exhibited over a broad range of combination therapies, and thus is broadly applicable to HER2 combination therapies in general. Further, Gemcitabine produces enhanced cytotoxicity in cells which over express HER2, and is ideal for combination therapy, as set forth above. Thus the demonstration post-

filing that the combination of Gemcitabine and an anti-HER2 monoclonal antibody exhibits synergistic anti-tumor effects is not sufficient to overcome the rejection, because it would be expected that HER-2 exhibits synergistic cytotoxicity with Gemcitabine.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set

forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

November 18, 2001

Sheela G Huff

SHEELA HUFF
PRIMARY EXAMINER